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# Side Effects of Neoadjuvant Chemotherapy for Nasopharyngeal Carcinoma

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**Abstract**

***Introduction:*** Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma of the mucosal nasopharynx with a unique geographical distribution which particularly prevalent in the east and southeast Asia. While nasopharyngeal carcinoma is a highly radiosensitive tumor, chemotherapy is added to enhance the effect of treatment. The therapeutic side effect is one of many factors that need to be considered when choosing the treatment method. Therefore, this study is conducted to address the side effect of neoadjuvant chemotherapy.
***Objective:*** This study is conducted to address the side effect of neoadjuvant chemotherapy.
***Methods:*** This study was a retrospective cohort study with total sampling method of all NPC patients in Hasan Sadikin General Hospital 2015-2019 period.
***Results:*** From a total of 247 subjects, NPC occurred in 180 men (72.87%). The most widely used regimen was Cisplatin + 5FU which is used in 187 patients (75.70%). There were several side effects caused by NPC chemotherapy including vomiting, nausea, fatigue, weight loss, dermatitis, stomatitis, hepatotoxicity, ototoxic, diarrhea, leucopenia, neutropenia, thrombocytopenia, and anemia.
***Conclusion:*** The most common side effect of cisplatin+5FU were ototoxicity therefore, audiometric examination both before and after administration of chemotherapy. Laboratory examination was needed for the administration of carboplatin+paclitaxel to monitor the side effects of neutropenia.

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## 1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma (SCC) arising from the mucosal surface of the nasopharynx [1]. It is characterized by a geographical distribution which particularly prevalent in the east and southeast Asia [2]. Generally, the incidence in the world less than 1 per 100,000 person-years [3]. More than 80% of NPC patients are in Asia, with 71% of new NPC cases are recorded in East and Southeast Asia [4]. In the endemic population, NPC risk factors Epstein-Barr virus (EBV) infection, environmental factors, such as the high intake of foods that rich in nitrosamines (preserved foods and salted fish), smoking, and genetic predisposition [3].

In 2012, an amount of 86,691 cases and 50,831 deaths of NPC had been documented in the world with sex ratio (male to female) of NPC risk about 2:36 and sex ratio (male to female) of NPC deaths about 2:37. The highest number of NPC cases was seen in five countries, such as China, Indonesia, Vietnam, India, and Malaysia [5]. In Indonesia, NPC are the fourth most common tumor after cervical cancer, breast cancer, and skin cancer and the most common malignancy in the head and neck [6]. It is a major burden in Indonesia, with 15,000 new cases a year [7].

While NPC is a highly radiosensitive tumor, chemotherapy is added to enhance the effect of radiation in locally advanced nasopharyngeal cancer because 70% of patients present with locally advanced stage and 5-year survival with RT alone are poor [8]. Nasopharyngeal carcinoma has been considered to be not only radiosensitive but also chemo-sensitive and has shown a high response rate to various chemotherapeutic agents [9].

Many factors need to be addressed in order to choose a treatment method, such as cancer itself, chemosensitivity or chemoresistance, cell population, growth cycle, the body's immune system, and therapeutic side effects [10]. Chemotherapy is defined as the application of chemicals or drugs to kill cancer cells, and its effects are systemic [11]. There are three main ways of combining systemic chemotherapy and radiotherapy; the classic combination ways include the induction (or neoadjuvant) chemotherapy before definitive radiotherapy and the adjuvant chemotherapy following definitive radiotherapy [12].

Neoadjuvant chemotherapy is defined as any chemotherapy regimen received prior to concurrent chemoradiotherapy [13]. Neoadjuvant chemotherapy agents commonly consist of platinum-based in combination with one of the following drugs: 5-fluorouracil, gemcitabine, paclitaxel, and docetaxel. Other drugs such as capecitabine, irinotecan, doxorubicin, vinorelbine, and oxaliplatin can also be used alone or in combination [14].

A study shows that neoadjuvant chemotherapy plays an important role in distant control or delaying distant metastasis [12]. Some studies also indicated that neoadjuvant chemotherapy docetaxel-cisplatin, followed by concurrent chemoradiotherapy (CCRT), had improved overall survival than CCRT alone in stage III to IVB NPC patients [15].

Nausea and vomiting, myelosuppression, anemia, and renal impairment are common in patients receiving chemotherapy regimens [14]. The therapeutic side effect was one of many factors that need to be considered when choosing a treatment method [10]. Therefore, this study is conducted to address the side effect of neoadjuvant chemotherapy.

## 2. MATERIALS AND METHODS

This is a retrospective cohort study conducted in June 2020. The subjects of this study were patients with NPC that has been treated with neoadjuvant chemotherapies in Hasan Sadikin Hospital 2015-2019 period. The data was taken from medical records with a total sampling method. The subjects of this study were NPC patients who underwent three cycles of chemotherapy to complete. Patients who have previously undergone a cycle of chemotherapy but are required to repeat the cycle were excluded. The data taken from medical records are patients characteristics, the regiment of neoadjuvant chemotherapy, and the side effects after each cycle.

## 3. RESULTS

During the period of the study, there were 247 subjects, with 180 (72.87%) were male and 67 (27.13%) were female. Most of the subjects were age 35-49 years. The distribution of subjects' characteristic is presented in table 1.

 

**Table 1.** Characteristic of the Subjects

| Characteristic | n | % |
|---|---|---|
| **Gender** | | |
| Male | 180 | 72.87 |
| Female | 67 | 27.13 |
| **Age** | | |
| 18-34 | 32 | 12.95 |
| 35-49 | 107 | 43.32 |
| 50-64 | 98 | 39.68 |
| >65 | 10 | 4.05 |
| **Stage** | | |
| 1 | 0 | 0 |
| 2 | 38 | 15.38 |
| 3 | 129 | 52.22 |
| 4 | 52 | 32.38 |
| **Histopathology (WHO Classification)** | | |
| Type I – Squamous cell carcinoma | 16 | 6.47 |
| Type II – Keratinizing undifferentiated carcinoma | 47 | 19.03 |
| Type III – Non-Keratinizing undifferentiated carcinoma | 184 | 74.49 |
| **Total** | **247** | **100** |

Table 2 shows that there were 2 regiments of neoadjuvant chemotherapy has been used in this study, with the most regiment used was Cisplatin+5FU.

**Table 2.** Regiments

| Neoadjuvant Regiments | n | % |
|---|---|---|
| Cisplatin+5FU | 187 | 75.70 |
| Carboplatin+Paclitaxel | 60 | 24.30 |
| **Total** | **247** | **100** |

Table 3 shows all of the side effects from neoadjuvant chemotherapy used was Cisplatin+5FU in NPC patients.

**Table 3.** Side effects of Cisplatin+5FU

| Side effects | 1st Cycle | | 2nd Cycle | | 3rd Cycle | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Vomiting | 14 | 7.49 | 9 | 4.81 | 6 | 3.21 |
| Nausea | 60 | 32.09 | 54 | 28.88 | 38 | 20.32 |
| Fatigue | 122 | 65.24 | 97 | 51.87 | 64 | 34.22 |
| Weight loss | 66 | 35.29 | 67 | 35.83 | 75 | 40.11 |
| Dermatitis | 6 | 3.21 | 8 | 4.28 | 11 | 5.88 |
| Stomatitis (mucositis) | 5 | 2.67 | 5 | 2.67 | 3 | 1.60 |
| Hepatotoxicity | 42 | 22.46 | 56 | 29.95 | 83 | 44.39 |
| Ototoxic | 18 | 9.63 | 69 | 36.90 | 107 | 57.22 |
| Diarrhea | 35 | 18.72 | 13 | 6.95 | 1 | 0.53 |
| **Hematologic** | | | | | | |
| Leucopenia | 19 | 10.16 | 31 | 16.58 | 35 | 18.72 |
| Neutropenia | 36 | 19.25 | 68 | 36.36 | 56 | 29.95 |
| Thrombocytopenia | 1 | 0.53 | 4 | 2.14 | 6 | 3.21 |
| Anemia | 5 | 2.67 | 8 | 4.28 | 15 | 8.02 |

Table 4 shows all of the side effects from neoadjuvant chemotherapy used was Carboplatin+Paclitaxel in NPC patients.

**Table 4.** Side effects of Carboplatin+Paclitaxel

| Side effects | 1st Cycle | | 2nd Cycle | | 3rd Cycle | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Vomiting | 12 | 20.00 | 10 | 16.67 | 4 | 6.67 |
| Nausea | 11 | 18.33 | 6 | 10.00 | 5 | 8.33 |
| Fatigue | 15 | 25.00 | 9 | 15.00 | 10 | 16.67 |
| Weight loss | 8 | 15.00 | 11 | 18.33 | 15 | 25.00 |
| Dermatitis | 5 | 8.33 | 7 | 11.67 | 9 | 15.00 |
| Stomatitis (mucositis) | 2 | 3.33 | 2 | 3.33 | 1 | 1.67 |
| Hepatotoxicity | 3 | 5.00 | 6 | 10.00 | 8 | 13.33 |
| Ototoxic | 6 | 10.00 | 8 | 13.33 | 11 | 18.33 |
| Diarrhea | 2 | 3.33 | 0 | 0.00 | 0 | 0.00 |
| **Hematologic** | | | | | | |
| Leucopenia | 9 | 15.00 | 16 | 26.67 | 34 | 56.67 |
| Neutropenia | 8 | 13.33 | 11 | 18.83 | 27 | 45.00 |
| Thrombocytopenia | 1 | 1.67 | 2 | 3.33 | 4 | 6.67 |
| Anemia | 2 | 3.33 | 3 | 5.00 | 7 | 11.67 |

## 4. DISCUSSIONS

A study conducted in 2018 found that in Indonesia, NPC is a relatively high incidence and more common in males [16]. Different lifestyle habits between men and women (e.g., tobacco consumption) or biological differences may be the cause [17]. In table 1, the data shows that many NPCs occur at the age of 35-49 years. This contrasts with a study in 2016, which stated that the peak age of incidence is between 50 and 60 years [18]

Table 1 shows that the most common stage of the cases was stadium 3 (52.22%) and 4 (32.38%). The most common histopathologic characteristic of the cases was type III (74.49%). This is supported by a study which also stated that the most common histopathologic characteristic of the cases was non-keratinizing undifferentiated carcinoma [19].

Evaluation after giving chemotherapy in the first cycle showed that fatigue was the most common side effect experienced by patients with a total of 137 (55.46%). This is supported by a study that states that fatigue is found in 52.4% of patients and is the most side effect in NPC patients [20].

The number of patients who experience side effects such as vomiting, nausea, fatigue, dermatitis, stomatitis, and diarrhea decreases from the first to the third cycle. This decrease may be due to the body's ability to adapt to the amount of chemotherapy received. Meanwhile, side effects such as weight loss, ototoxic, leucopenia, neutropenia, thrombocytopenia, and anemia actually show an increase as the chemotherapy cycle progresses.

The most common side effects of cisplatin+5FU in the third cycle were ototoxicity. The mechanistic basis for ototoxicity induced by cisplatin is not fully understood yet, but cisplatin is known to damage the organ of Corti, the spiral ganglion, and the stria vascularis as primary targets. Administration of antioxidants plays an important role in preventing ototoxicity due to cisplatin chemotherapy, pure tone audiometry should be examined prior to chemotherapy, and after chemotherapy [21]. The most common side effects of carboplatin+paclitaxel in the third cycle were leucopenia. Therefore, laboratory examination was needed to be carried out before and after chemo carboplatin.

## 5. CONCLUSION

The most common side effect of cisplatin+5FU were ototoxicity, therefore an audiometric examination both before and after administration of chemotherapy. Laboratory examination is needed for the administration of carboplatin + paclitaxel to monitor the side effects of neutropenia.

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